What's wrong with the amygdala in temporal lobe epilepsy?

The amygdala has long been implicated in the semiology of temporal lobe epilepsy. John Hughlings Jackson's (1880) earliest description of the 'dreamy state' published in *Brain* stresses the sensations of terror and anger, as well as the premonitory and epigastric sensations, olfactory hallucinations and automatic behaviours that we recognize as features of complex partial seizures arising in the temporal lobe. It is tempting to think of affective symptoms as separate from the *déjà vu* and premonitions that imply involvement of the hippocampal formation. However, Gloor *et al*. (1982) showed that stimulation in the amygdala could elicit a full spectrum of experiential symptoms in patients with intractable temporal lobe epilepsy, even when after-discharges implying stimulus spread were not seen. More recently the term 'dysphoric disorder of epilepsy' has been proposed to describe a combination of emotional instability, dysphoria, irritability and aggression, and associated decreases in amygdalar volume suggest a causal link to abnormalities of this nucleus (van Elst *et al*., 2009). But what are these abnormalities? How do they relate to either ictal or interictal affective symptoms? And what is the role of the amygdala in the initiation, spread and termination of seizures in temporal lobe epilepsy? Answers to these questions are still far off, but the study reported by Graebenitz and colleagues in this issue of *Brain* (page 2929) provides a glimpse into possible links among these phenomena.

Although selective amygdalotomy has, in the past, been promoted as effective treatment for temporal lobe epilepsy (Feindel and Rasmussen, 1991), it is currently reserved for patients with suspected epileptogenic lesions confined to the temporal pole and sparing the hippocampus. Nevertheless, some evidence suggests that anterior temporal pole resections that include the amygdala yield a higher rate of seizure freedom than selective hippocampectomy (Schramm, 2008). Anterior temporal lobectomy has therefore become the standard surgical procedure for refractory temporal lobe epilepsy, and the study by Graebenitz and co-workers reports on a broad range of parameters measured *ex vivo* from the amygdala in patients who underwent this operation for intractable temporal lobe epilepsy.

Histological analysis of resected tissue has already provided invaluable information on the selective vulnerability of different cell types in the amygdala, much of which mirrors changes seen in rodent epilepsy models (Pitkänen *et al*., 1998). The selective loss of some interneurons, especially those expressing somatostatin, recapitulates changes seen in the hippocampus. This general area of research has also highlighted a paradox: because mesial temporal sclerosis is characterized by widespread loss of excitatory pyramidal neurons, in particular in the CA3 and CA1 subfields, how do seizures arise in, or propagate out of, the hippocampus? Shifting attention to the subiculum (which is innervated by CA1 pyramidal neurons), principal neurons have recently been shown to discharge spontaneously in *ex vivo* tissue slices incubated in oxygenated artificial cerebrospinal fluid, with evidence for a paradoxical depolarizing effect of GABAergic signalling (Cohen *et al*., 2002). It is, of course, not possible to 'prove' that cellular and circuit phenomena identified in human tissue studied *ex vivo* are the cause of seizure initiation, not least because control tissue is, to all intents, unobtainable. Nevertheless, parallel studies on rodent models of limbic epilepsy have uncovered numerous molecular and cellular alterations, and progress will no doubt depend on convergence between these areas of research.

What about the amygdala? This nucleus typically undergoes much less sclerosis than the hippocampal formation, and it can rarely be enlarged in patients without ipsilateral hippocampal sclerosis (Mitsueda-Ono *et al*., 2011). Graebenitz and colleagues report spontaneous discharges in the lateral amygdala recorded *in vitro* especially in those cases where sclerosis was minimal. The lateral amygdala is an output nucleus of the amygdala that projects widely to the temporal neocortex and hippocampus. Although it is impossible to know whether spontaneous discharges would also have been seen in non-epileptic tissue, rodent studies have shown that they occur in the lateral amygdala of epileptic but not control animals (Benini and Avoli, 2006). Do these discharges reflect a propensity for seizure initiation in the amygdala? In two patients interictal spikes, spike-wave and polyspike complexes were seen intra-operatively in the amygdala, but the data do not allow one to conclude that they originated in this nucleus.

Brief spontaneous discharges observed *in vitro* are more reminiscent of interictal spikes than seizures *per se*, and have been shown in human neocortex to depend on both fast glutamatergic and GABAergic signalling (Köhling *et al*., 1998). The discharges recorded by Graebenitz and colleagues share this pharmacological profile. However, recent studies have shown that the build-up to overt seizure-like discharges in the subiculum and neocortex *in vitro* is associated with a collapse of inhibition (Trevelyan *et al*., 2007; Huberfeld *et al*., 2011). It is, however, notoriously difficult to elicit seizure-like activity in tissue from epileptic humans or rodents (Cohen *et al*., 2002; Gabriel *et al*., 2004; Zahn *et al*., 2008), possibly explained by the degree of sclerosis of the tissue. Indeed, Graebenitz and co-workers also found that spontaneous discharges were less likely to occur in sclerosed tissue.

Interestingly, the amygdala of several species is extremely susceptible to electrical kindling (Goddard *et al*., 1969). This is a long-established animal model of epileptogenesis that relies on the finding that intermittent stimuli elicit electrographic seizures at progressively lower threshold. Whether this susceptibility of the amygdala to kindling reflects use-dependent synaptic plasticity in the intrinsic circuit or vulnerability of inhibition remains to be determined.

A clue to changes in signalling mechanisms in the amygdala comes from quantitative analysis of the expression of several

neurotransmitter receptors. In this case, because live tissue does not need to be harvested, it is possible to compare with non-epileptic post-mortem temporal lobe samples (bearing in mind possible differences in tissue processing and alterations that might reflect long-term exposure to anti-epileptic drugs). Graebenitz and colleagues report an overall increase in the density of several excitatory glutamate receptors in the lateral amygdala, including the AMPA and kainate subtypes, blockade of which abolish spontaneous discharges. They also observe changes in several muscarinic, noradrenergic and serotonergic receptors, whose effects on excitability are generally more subtle. As for $GABA_A$ receptors, which were also implicated in the generation of spontaneous activity, Graebenitz *et al*. report a dissociation between the binding of the agonist muscimol (which was not altered significantly) and of the antagonist SR95531 (also known as gabazine, which was decreased). The authors interpret this discrepancy within the context of differences between agonists and antagonists binding to active and inactive forms of receptors. An alternative possible explanation for this dissociation is that SR95531 has a higher affinity for subtypes of $GABA_A$ receptors that tend to be continuously active, and which contribute to so-called 'tonic inhibition' (Semyanov *et al*., 2004). Either way, the results imply an overall decrease of $GABA_A$ receptor-mediated signalling.

Taken together with the evidence for loss of interneurons, the occurrence of spontaneous discharges and changes in receptor expression point to a net shift towards a disinhibited state. Although the conceptual usefulness of 'excitation-inhibition balance' in a phenomenon as complex as seizure initiation can be questioned, the report by Graebenitz *et al.* is an important addition to our understanding of the role of the amygdala in temporal lobe epilepsy.

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